REMARKS

The Office Action of April 3, 2009, has been received and reviewed. All claims stand rejected. This application is to be amended as previously set forth. All amendments and claim cancellations are made without prejudice or disclaimer. Basis for the amendments can be found in the original claims. Basis for the new claims can be found throughout the application, but particularly in paragraphs **[0014]**, **[0033]**, and **[0041]**. No new matter has been presented. Reconsideration is respectfully requested.

Personal Interview

Applicant thanks the Office for the courtesy extended applicant and applicant's representatives at the personal interview scheduled on Thursday, July 9, 2009 at 9:00 a.m. Attending the interview were the named inventor, Dr. Lothar Steidler, a representative of the assignee, Emil Pot, and the undersigned, Allen C. Turner. Attending on behalf of the Office was Examiner Prouty.

As set forth in the Examiner Interview Summary, all pending claims were discussed as was all of the prior art of record.

Although no agreement was reached, at the interview,

> Applicant argued the deficiencies of the Nilsson reference particularly with regard to a teaching of use of a thyA mutant for production of a therapeutic protein and viability with the environment of the intestines. Examiner [countered] however, that the rejection was not made over Nilsson alone and that the other references provide the teachings to suggest these features, in particular the Curtiss reference clearly suggest that thyA mutants are, in fact, viable within the intestinal mucosa Applicant argued that the mouse used by Curtiss is a system which is unusually rich in thymidine and thus not a good model for success in any mammal. Examiner requested that applicant provide some references to support this statement. Applicant argued that Curtiss does not need viability of the mutant for success and thus while Curtiss shows data that make it clear that at least some of [Curtiss'] thyA mutant cells were viable, this could have been achieved even if only a very small percentage of the thyA cells of Curtiss were viable as even dead cells can have an antigenic effect, but availability is critically important for the instant mutants. Finally, Applicant argued that Curtiss teaches that use of thyA mutants actually enhanced the immunogenic effect of the antigenic protein and thus would teach away from using a thyA mutant expressing a therapeutic protein instead of an antigenic protein as immunogenicity would be detrimental to successful therapeutic use. Examiner asked that applicant point to where Curtiss

> teaches this enhancement of immunogenicity. Examiner indicated that in total applicant's arguments appear convincing but that she would like to see them presented along with the requested information in order to fully evaluate whether to withdraw the 103 rejection.

Applicant believes that the foregoing statement (which is a slightly revised version of the Examiner's statement), taken together with the contents of this Amendment, adequately sets forth the substance of the interview. If, however, the Office believes that more detail would be beneficial, the Office is kindly requested to contact applicant's undersigned attorney, and more detail will be provided to the extent available.

Claim objections

Claim 14 stands objected to under 37 C.F.R. § 1.75(c) as assertedly being in improper multiple dependent form. Applicant has amended claim 14 to alter the dependency, and respectfully requests the objection to claim 14 be withdrawn.

Claim 34 stands objected to under 37 C.F.R. § 1.75(c) as assertedly failing to further limit the subject matter of claim 32, from which it depends. Applicant has amended claim 32 to recite, wherein altering the *Lactococcus* thymidylate synthase gene to inactivate the *Lactococcus* thymidylate synthase encoded thereby comprises gene disruption. Applicant has also amended claim 34 to recite, wherein the gene encoding said heterologous therapeutic molecule is integrated within, or replaces at least a part of the thymidylate synthase gene. Gene disruption can occur by other than integration of a therapeutic molecule, or replacement of the disrupted gene. For example, gene disruption can be accomplished by introducing a stop codon in the gene, by introducing inactivating point mutations, by introducing a frame shift mutation, or by inactivating the promoter or other regulatory sequences. Therefore, applicant respectfully submits that amended claim 34 does further limit the subject matter of amended claim 32, and applicant respectfully requests that the objection be withdrawn.

Claims 22, 32, and 67 are objected to for various informalities. Applicant has amended these claims per the Office's suggestions, and applicant thus respectfully requests that these objections be withdrawn.

35 U.S.C. § 112, second paragraph

Claims 1-3, 5-7, 10, 12, 13, 15, 17, 22, 31, 65, and 68 stand rejected under 35 U.S.C. § 112, second paragraph, as assertedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant has amended the claims and respectfully requests that the rejection be withdrawn.

First, it was asserted that "Claims 1, 22, 31 and 68 (upon which claims 2, 3, 5-7, 10, 12, 13, 15, 17, and 65 depend) are confusing in the recitation of 'said strain' as it is unclear if this refers to the *thyA* mutant strain or the parent *Lactococcus* strain prior to mutation." As agreed at the interview, applicant has amended the claims to clarify the situation, and respectfully request that the rejection be withdrawn.

In the Office Action, the Office further asserted, "Claims 5 and 65 (upon which claims 6, 7, 10, 13, 15, 17, and 68 depend) are confusing in the recitation of 'further transformed[']' as the *thyA* mutant strain of claim 1 is not recited as a transformed strain. Thus it is not clear how it can be further transformed." Id., at page 4. Applicant has amended claims 5 and 65 to remove the word "further." As amended, claims 5, 6, 7, 10, 13, 15, 17, 65, and 68 are not indefinite.

For at least the foregoing reasons, applicant respectfully requests the rejections of these claims under 35 U.S.C. § 112, second paragraph, be withdrawn.

35 U.S.C. § 112, first paragraph

Claim 68 stands rejected under 35 U.S.C. § 112, first paragraph, as assertedly failing to comply with the enablement requirement by assertedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Applicant respectfully traverses this rejection.

Claim 68 was rejected for reciting *Lactococcus* strain MG1363. MG1363 is well-known and widely-available in the art. For example, a search of NCBI's "PubMed" database using the search term, "MG1363," reveals an abundance of research from disparate groups using said *Lactococcus* strain. Also, GenBank has a record of the organism's complete genome. Therefore, *Lactococcus* strain MG1363 is "publicly known and freely available." However, if *Lactococcus* strain MG1363 is unavailable through, *e.g.*, ATCC or the strain is otherwise unavailable, and this is the last remaining obstacle to allowing the application, a deposit will be made.

Rejections under 35 U.S.C. § 103(a)

Claims 1-3, 5-7, 10, 12, 13, 15, 17, 21, 23-26, 29, 30, 32, 34, 35, 37-39, 42, and 65-67 stand rejected under 35 U.S.C. § 103(a) as assertedly being unpatentable over Nilsson *et al.* (2000) WO 00/01799 (hereinafter "Nilsson"), in view of Steidler *et al.* (2000) WO 00/23471 (hereinafter "Steidler") and Curtiss III (1989) U.S. Patent 4,888,170 (hereinafter "Curtiss"). Applicant respectfully traverses this rejection.

The rejected claims are patentable over Nilsson in view of Steidler and Curtiss for at least the reason that the combination of Nilsson, Steidler, and Curtiss for at least the reasons that: (1) no motivation would have existed to combine the references in the manner presently claimed; (2) Nilsson and Curtiss teach away from the proposed combination; (3) the proposed combination would impermissibly change Curtiss' and Nilsson's principles of operation; and (4) secondary considerations weigh in favor of non-obviousness with respect to the claimed subject matter.

To establish a *prima facie* case of obviousness, the prior art itself or "the inferences and creative steps that a person of ordinary skill in the art would [have] employ[ed]" at the time of the invention are to have taught or suggested the claim elements. Additionally, there is to have been "a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742, 167 L.Ed.2d 705, 75 USLW 4289, 82 USPQ2d 1385 (2007). "Often, it will be necessary for a [fact finder] to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed. . . . To facilitate review, this analysis should be made explicit." *Id.* "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness". *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). Furthermore, to establish a *prima facie* case of obviousness, there must have been a reasonable expectation of success. M.P.E.P. § 2143.02. Underlying the obvious determination is the fact that statutorily prohibited hindsight cannot be used. *KSR*, 127 S.Ct. at 1742.

No motivation would have existed at the time of the invention to combine Nilsson, Steidler, and Curtiss to arrive at the claimed *Lactococcus* mutant that comprises a gene encoding a heterologous therapeutic molecule and expresses the molecule

All of the claims currently under consideration are drawn to *thyA* mutants of *Lactococcus* comprising a gene encoding and expressing a heterologous therapeutic molecule. As noted by the Office, "The *thyA* mutant strain of Nilsson et al. differs from that claimed in that it does not comprise a heterologous gene encoding a therapeutic protein." Office Action, at page 6. Further, the *thyA* mutant strain of Nilsson does not express a therapeutic molecule. The pending claims are patentable over Nilsson, Steidler, and Curtiss for at least the reason that the thyA mutant of Nilsson was developed for a completely different purpose than the present invention, and there would have been no motivation to lead one of skill in the art from this unlikely starting point to the subject matter of the present claims.

Nilsson teaches a *thyA* inactivation mutant of the *Lactococcus* strain MBP71, produced by homologous recombination. Nilsson does not provide any direction towards a gene encoding a therapeutic molecule. Moreover, it is precisely the presence of a gene encoding a therapeutic protein that accomplishes an objective of the present invention; to provide biological containment upon therapeutic protein delivery. Nilsson's *thyA* mutant was generated for a completely different and non-analogous reason, *i.e.*, to convey bacteriophage resistance.

As stated in Nilsson, "Bacteriophages require hosts with intact DNA replication, RNA transcription and protein synthesis in order to become proliferated. Accordingly, bacterial cultures used in the method of the invention are incapable of performing one of the above activities, which makes such bacterial cultures substantially completely resistant to attack by bacteriophages." Id., at col. 7, line 31, through col. 8, line 1.

Steidler teaches the use of a cytokine-producing *Lactococcus* strain to treat colitis, *i.e.*, delivery of IL-10 using *Lactococcus*, but Steidler is silent with respect to *thyA* and *Lactococcus* containment.

Curtiss relates to vaccines obtained from antigenic gene products of recombinant genes, and is not even thought to mention *Lactococcus*. In particular, Curtiss relates to avirulent derivatives of pathogenic microbes, *i.e., Salmonella or Salmonella-E coli hybrid.* Moreover, Curtiss' work is performed in a mouse model. A mouse model is recognized by those of skill in

the art as a particularly poor system for extrapolating results to mammals in general, as mice are a system unusually rich in thymidine. See, *e.g.*, Nottebrock and Then (1977), at page 2177, Table 2 (submitted in accompanying Supplemental Information Disclosure Statement).

As discussed at the interview, the object of Curtiss' invention is to raise an immune response to the protein delivered by the bacteria. See, *e.g.*, col. 5, lines 56-59 ("If these carrier bacteria contain and express a recombinant gene from a pathogenic organism, *antibodies against the antigenic gene product produced from the pathogen will be induced.*") (emphasis added; note also that all microbes able to be used in Curtiss' invention must be pathogenic, as explained below on page 16 hereof); see also, col. 1, lines 46-49 ("Enhancing the immune response of the secretory system is thus a desirable goal in inducing immunity against microbial pathogens"); col. 12, lines 43-50 ("the microbe expresses the gene to produce a gene product capable of inducing antibodies"); col. 7, lines 24-48 ("a carrier of the gene product which is used for stimulating antibody response"); col. 3, lines 15-20 ("said gene is expressed in a second organism which produces said gene product and wherein said gene product induces an immune response in said animal").

Moreover as would be readily appreciated by one of ordinary skill in the art, Curtiss particularly shows at column 20 that immunogenicity increases with *thyA* inactivation. For example, in Tables III, IV, and V, Curtiss reports the antibody response in mice challenged with various strains of *S. typhimurium* expressing *S. mutans* antigens. As set forth at cols. 17 and 18 and Table II of Curtiss, strains χ3137 and χ3115 contain an inactivating mutation of the *thyA* gene. Compared to control strain χ3245, which does not contain a *thyA* mutation, the peak antibody titer from saliva (at 22 days post challenge) is 10-fold higher in mice challenged with χ3137, which does contain a *thyA* mutation. (Compare Tables III and IV in Curtiss). Further, the peak antibody titer from serum is nearly 10-fold higher in mice challenged with thyA mutant strain χ3115 than strain χ3245. (Compare Tables III and V in Curtiss). (See, also, Curtiss, column 2, lines 64-68 "It is . . . [an] object of the invention to provide a vaccine that will . . . stimulate the production of IgA in the secretory system with a concomitant stimulation of the humoral and cellular immune responses.") The last thing one would want in delivering a therapeutic molecule, however, is increased immunogenicity. Curtiss thus teaches away from applicant's invention.

In the Office Action, the Office asserted, "One of skill in the art would have been motivated to select the thyA mutant strain of Lactococcus lactis of Nilsson et al. as the host strain for the therapeutic delivery by the disclosure of Curtiss III that for administration of genetically engineered bacteria that are intended to produce a heterologous protein in the intestinal mucosa of the animal alteration of the microorganism such that it is incapable of surviving in nature but still capable of delivering the heterologous protein to the intestinal mucosa is preferable and the *thyA* mutant strains are examples of such strains." Id., at pages 7-8. By this statement, the Office seems to suggest that Curtiss' teaching of expression of an antigen provides a motivation to express a therapeutic protein. More generally, the Office seems to suggest that Curtiss teaches a general motivation towards containment of bacterial vectors, and therefore that since *thyA* mutants work for this purpose, *thyA Lactococcus* mutants that are contained are obvious. Applicant respectfully disagrees. As stated, *supra*, applicant can find no passage in Curtiss that would guide one of skill in the art to apply its teachings to the administration of bacterial vectors expressing therapeutic proteins. Curtiss discusses bacteria suitable for use in a vaccine, for example, at col. 9, lines 4-48, within the context of disclosing a means for releasing antigen such that it is "available to the animal's immune system." Curtiss, at col. 9, lines 4-6.

Further, Curtiss relates to vaccines against infection, in which the carrier must be a *pathogenic* microbe (Id., *e.g.*, description of the prior art; Table I; col. 2, line 55; col.3, line 4; col. 4, line 28; col. 6, line 39; and col. 7, line 24), where *homing* to GALT or BALT is essential to improved immunogenicity. The pathogenicity is an essential feature for the homing to GALT or BALT. Id., Table 1, col. 6, line 39 through col. 7, line 24; see also col. 19, lines 51-55 ("Comparable studies with the avirulent *S. typhi* Ty21a derivative χ3175 expressing synthesis of the *S. mutans* SpaA protein, cannot be performed in mice since *S. typhi* is not a pathogen for mice"). The present invention does not relate to pathogenic microbes or to avirulent microbes. *Lactococcus* is not pathogenic. Consequently, there can be no intention to make *Lactococcus* avirulent. Thus, there is no need in view of Curtiss for making a *thyA* deficient strain of *Lactococcus*. Thus, the skilled artisan would not find in Curtiss any motivation to arrive at the presently claimed subject matter.

Moreover, merely because applicant has made the valuable discovery that *thyA Lactococcus* mutants are particularly well-suited as vectors for providing containment during the

delivery of therapeutic proteins does not mean that the use of *thyA Lactococcus* mutants in this application was therefore obvious. While "[a]n 'obvious to try' rationale may support a conclusion that a claim would have been obvious where one skilled in the art is choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success," MPEP § 2145(X)(B), this rationale fails when what would have been obvious to try was to "try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical *or no direction as to which of many possible choices is likely to be successful.*" Id. (emphasis added).

Without the benefit of impermissible hindsight from applicant's disclosure, it was not predictable that *thyA* mutant *Lactococcus* would have the attributes that applicant has disclosed. There were innumerable possibilities for mutant bacteria to be used in the claimed compositions and methods. There is no direction given in Nilsson, Steidler, or Curtiss as to which of the many possible mutant bacteria would be useful in accomplishing containment in the context of delivering therapeutic proteins.

Because there was no motivation at the time the present invention was made for one of skill in the art to produce a *thyA* mutant *Lactococcus* to deliver therapeutic proteins such that those mutant *Lactococcus* would be contained, either in the form of specific direction toward such a mutant or as one of countless available options, the pending claims are patentable over Nilsson, Steidler, and Curtiss.

Nilsson and Curtiss teach away from the use of *thyA* mutant *Lactococcus* in drug delivery, wherein the mutant Lactococcus are contained

A claim is not obvious in view of a reference that teaches away from the claim. MPEP §§ 2144.02(VI) and 2145(X)(D)(2); W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). Moreover, a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Baird, 16 F.3d 380 (Fed. Cir. 1994). A reference is said to "teach away" when a person of ordinary skill, upon reading it, would be discouraged from following the path set out in the reference, "or would be led in a direction divergent from the path taken by the inventor." In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994); Monarch Knitting Mach. Corp. v. Sulzer Morat Gmbh, 139 F.3d 877 (Fed. Cir.

1998); Para-Ordnance Mfg. v. SGS Importers Int'l Inc., 73 F.3d 1085 (Fed. Cir. 1995).

As noted, *supra*, the pending claims are drawn to isolated *thyA* mutants of *Lactococcus* comprising a gene encoding a heterologous therapeutic molecule. It is an important feature of such mutant *Lactococcus* for the purpose of the present invention that they be "contained". As stated in the Specification, "Such a *Lactococcus* sp. *thyA* mutant is very useful as a host strain for transformation in situations where more severe containment than purely physical containment is needed. Indeed, *thyA* mutants cannot survive in an environment without or with only a limited concentration of thymidine and/or thymine. When such a strain is transformed with a plasmid that does not comprise an intact *thyA* gene and cannot complement the mutation, the transformed strain will become suicidal in a thymidine/thymine-poor environment." Id., at **[0029]**. Applicant then presents data in the Specification that shows depletion of thymidine results in decrease of colony-forming mutant bacterial units. Id., at FIGs. 10 and 11; **[0048]**.

In related work published by applicant, the susceptibility of *thyA* mutant *Lactococcus* to thymidine deprivation was investigated, and the results reinforce the teachings of the present disclosure. Steidler *et al.* (2003) Biological containment of genetically modified *Lactococcus lactis* for intestinal delivery of human interleukin 10, Nature biotechnology 21(7):785-89 (Submitted in accompanying Supplemental Information Disclosure Statement). Applicant's published research demonstrates conclusively that "(t)he survival of thyA-deficient strains depends on the presence of thymidine or thymine in the growth medium." Steidler (2003), at 786. "(R)apid death occurs upon thymidine starvation." Id., at 788. Hence, one of skill in the art could not combine a reference which teaches that thyA mutants remain viable in thymidine-poor environments to arrive at applicant's invention.

Containment of *thyA Lactococcus* mutants by thymidine deprivation is wholly incompatible with the explicit teachings of Nilsson. Importantly, Nilsson does not introduce a *thyA* mutation to induce death in the resulting *Lactococcus* mutant under low thymidine conditions, such as is necessary for the confinement of the bacteria, but for the purpose of permitting metabolism by *live* mutants in low thymidine conditions without bacteriophage attack. See, *e.g.*, Id., at col. 9, lines 18-25. Because Nilsson teaches that *thyA* mutant *Lactococcus* are not killed (which is how such bacteria may be contained) under conditions of low thymidine, but rather are viable while being protected against bacteriophages, one of skill in the art could not

have combined Nilsson with Steidler and Curtiss to arrive at the presently claimed subject matter.

As discussed, *supra*, Curtiss requires a pathogenic microbe for the purpose of its disclosed compositions and methods. The instant claims do not relate to pathogenic microbes or to avirulent microbes. *Lactococcus* is not a pathogenic microbe and is not disclosed in Curtiss. Consequently, Curtiss teaches further away from its combination with Nilsson and Steidler, where the presently claimed result is a *thyA Lactococcus* mutant. Furthermore, it is an object of Curtiss to provide vaccines yielding improved immunization. However, immunization is not desirable in the present claims. Immunization against a therapeutic protein, as used in delivery, would block the activity of the protein and render the composition ineffective.

For at least the foregoing reasons, Nilsson and Curtiss teach away from the claimed combination, and therefore cannot be used to make out a *prima facie* case the pending claims are obvious.

The combination of Nilsson and Curtiss into a contained *thyA Lactococcus* mutant impermissibly changes Nilsson's and Curtiss' principles of operation

Modifications of prior art references may only support a *prima facie* obviousness determination if a reasonable expectation of success existed in making the proposed modification. MPEP 2143.02(I); In re Merck & Co., Inc., 800 F.2d 1091 (Fed. Cir. 1986). There cannot be a reasonable expectation of success in making a proposed modification to a reference when the resulting modification would be inoperable. Similarly, a proposed modification to a reference may not change its principle of operation to support a rejection under 35 U.S.C. § 103. When a proposed modification would change the principle of operation of a reference, that reference may not be relied upon to make a *prima facie* obviousness determination. MPEP 2143.01(VI); In re Ratti, 270 F.2d 810 (CCPA 1959).

Even if the Office concluded that Nilsson and Curtiss do not teach away from the proposed combination, applicant notes that the proposed combination would impermissibly change the principles of operation inherent in these references. In Nilsson, it is an essential principle that the *thyA* mutants provided therein are able to survive in thymidine-depleted media. Nilsson, *e.g.*, at col. 9, lines 18-25. It is precisely because they do not die in such a depleted

environment that they are able to perform metabolic processes while being resistant to bacteriophage attack. To combine Nilsson to produce the pending claims requires imputing *thyA* mutant *Lactococcus* that die when removed from high thymidine; *i.e.*, the *Lactococcus* are contained. Under these circumstances, the *thyA* mutants would not be capable of performing their necessary metabolic functions within the teachings of Nilsson.

In Curtiss, it is an essential principle that pathogenic bacteria be used. As discussed, *supra*, homing to GALT or BALT is essential to the improved immunogenicity provided by the invention. And, the pathogenicity is an essential feature for the homing to GALT or BALT. Combining Curtiss to produce the present claims, where the mutant bacteria are *Lactococcus*, would eliminate the possibility of providing improved immunogenicity.

Moreover, there was no motivation to combine the references in the manner presently claimed; Nilsson and Curtiss teach away from the proposed combination; and the proposed combination would impermissibly change Curtiss' and Nilsson's principles of operation.

For at least the foregoing reasons, applicant respectfully requests the rejection of the claims under 35 U.S.C. § 103(a) be withdrawn.

Secondary consideration further support that the pending claims are not obvious

Secondary considerations must be evaluated by the Office when reconsidering a rejection under 35 § U.S.C. 103. MPEP § 2141(II); MPEP § 2145; Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17-18 (1966). Recognition by those of skill in the art of a need for an invention, and evidence of an invention's favorable reception by those of skill in the art are aspects of an invention's success. MPEP § 2145; In re Piasecki, 745 F.2d 1468, 1471 (Fed. Cir. 1984). The evidence may be provided in a timely manner at any point during prosecution. MPEP § 2141(II).

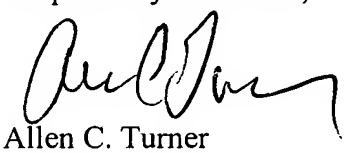
In the present case, applicant's invention has been widely acknowledged as a significant breakthrough in the field of providing therapeutic gene products via genetically modified microorganisms. It represents a giant leap forward from prior art methods of providing containment for such therapeutic vectors. As evidenced by the selection of applicant's work as a featured front-page article in *Nature Biotechnology*, applicant's work was recognized as extremely newsworthy. (Front page of July 2003 issue of *Nature Biotechnology* submitted in

accompanying Supplemental Information Disclosure Statement).

In the accompanying Supplemental Information Disclosure Statement, applicant has submitted several published reports of applicant's work. These reports praise the innovation and importance of applicant's invention, and note that a strain of genetically modified bacteria according to applicant's invention has been approved for "the first ever clinical trial of a live GM-bacteria-based experimental therapy in humans." Kitchener (2003). Bradbury (2003) describes the novelty, significance, and progress of these clinical trials. See, e.g., page 964, col. 3, through page 965, col. 1 ("it became clear that some way had to be found to deliver (IL-10) directly at the site of inflammation... The next step was to modify the genetically modified organism to prevent it escaping into the environment... now the mini IL-10 factories are being tested in people by van Deventer. Housed in a special isolation unit, 12 patients with Crohn's disease will be treated orally for 1 week with the genetically modified organism packaged in capsules designed to open in the small bowel. To date, says van Deventer, several patients have been treated and the trial is going well."). These reports provide secondary evidence showing that the presently claimed subject matter was not obvious at the time the invention was made.

The application should be in condition for allowance. If, however, questions remain after consideration of the foregoing, the Office is kindly requested to contact applicant's attorney at the address or telephone number given herein.

Respectfully submitted,



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Enclosures: Supplemental Information Disclosure Statement